

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT-1235

To:
LECLAIRE, FRANCE
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3ième etage, bureau 3950
MONTREAL, Quebec
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PCT

**NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY**
(Chapter II of the Patent Cooperation Treaty)

(PCT Rule 71.1)

Date of mailing: 29 November 2005 (29-11-2005)
(day/month/year)

Applicant's or agent's file reference
13664-40PCT

IMPORTANT NOTIFICATION

International application No.
PCT/CA2004/001409

International filing date (day/month/year)
26 July 2004 (26-07-2004)

Priority date (day/month/year)
25 July 2003 (25-07-2003)

Applicant
CONJUCHEM, INC. ET AL

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)). (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the *PCT Applicant's Guide*.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed invention is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the IPEA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| | | |
|--|---|--|
| Applicant's or agent's file reference 13664-40PCT | <div style="display: flex; justify-content: space-between;"> FOR FURTHER ACTION See Form PCT/IPEA/416 </div> | |
| International application No. PCT/CA2004/001409 | International filing date (day/month/year) 26 July 2004 (26-07-2004) | Priority date (day/month/year) 25 July 2003 (25-07-2003) |
| International Patent Classification (IPC) or national classification and IPC IPC(7): C07K 14/62, C07K 1/113, C07K 14/765, A61K 38/28, A61P 3/10, A61P 5/50, A61K 47/42 | | |
| Applicant: CONJUCHEM, INC. ET AL | | |
| <p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p style="margin-left: 20px;">a. <input checked="" type="checkbox"/> (sent to the applicant and to the International Bureau) a total of 10 sheets, as follows:</p> <p style="margin-left: 40px;"><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions);</p> <p style="margin-left: 40px;"><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. 1 and the Supplemental Box.</p> <p style="margin-left: 20px;">b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p> | | |
| <p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the report</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p> | | |
| Date of submission of the demand 18 May 2005 (18-05-2005) | Date of completion of this report 29 November 2005 (29-11-2005) | |
| Name and mailing address of the IPEA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Québec K1A 0C9 Facsimile No.: 001(819)953-2476 | Authorized officer Colleen MacFarlane (819) 997-4614 | |

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CA2004/001409

Box No. I Basis of the report

1. With regard to the language, this report is based on:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of:
 - ☐ international search (Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (Rule 12.4(a))
 - ☐ international preliminary examination (Rules 55.2(a) and/or 55.3(a))
2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:
 - ☐ the international application as originally filed/furnished
 - ☒ the description:
 - ☒ pages 2-26 as originally filed/furnished
 - ☒ pages* 1 and 1A received by this Authority on 18 May 2005
 - ☐ pages* _____ received by this Authority on _____
 - ☒ the claims:
 - ☐ pages _____ as originally filed/furnished
 - ☐ pages* _____ as amended (together with any statement) under Article 19
 - ☒ pages* 27-31 received by this Authority on 18 May 2005
 - ☒ pages* 32-34 received by this Authority on 26 October 2005
 - ☐ the drawings:
 - ☐ pages _____ as originally filed/furnished
 - ☐ pages* _____ received by this Authority on _____
 - ☐ pages* _____ received by this Authority on _____
 - ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.
3. ☒ The amendments have resulted in the cancellation of:
 - ☒ the description, pages 1
 - ☒ the claims, Nos. 1-38
 - ☐ the drawings, sheets/figs _____
 - ☐ the sequence listing (*specify*): _____
 - ☐ any table(s) related to sequence listing (*specify*): _____
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
 - ☐ the description, pages _____
 - ☐ the claims, Nos. _____
 - ☐ the drawings, sheets/figs _____
 - ☐ the sequence listing (*specify*): _____
 - ☐ any table(s) related to sequence listing (*specify*): _____

* If item 4 applies, some or all of those sheets may be marked "superseded."

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 23-31

because:

☒ the said international application, or the said claims Nos. 23-31

relate to the following subject matter which does not require an international preliminary examination (*specify*):

Although claims 23-31 encompass a method of treatment of the human/animal body which this Authority is not required to examine under Rule 67.1(iv) of the PCT, the IPRP has been established on the basis of the alleged effects of the polypeptides referred to therein.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it;

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it;

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b) and 13ter.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it;

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|-------------------------------|--------|-------------|-----|
| Novelty (N) | Claims | <u>1-37</u> | YES |
| | Claims | <u>NONE</u> | NO |
| Inventive step (IS) | Claims | <u>1-37</u> | YES |
| | Claims | <u>NONE</u> | NO |
| Industrial applicability (IA) | Claims | <u>1-37</u> | YES |
| | Claims | <u>NONE</u> | NO |

2. Citations and explanations (Rule 70.7)

Reference is made to the following documents:

D1: WO 95/05187 A1 (UNITED MEDICAL 7 DENTAL SCHOOLS OF GUY'S AND ST. THOMAS HOSPITALS)
D2: CA 2334859 A1 (KINGS COLLEGE LONDON; DEUTSCHES WOLFFORSCHUNGS INSTITUT)
D3: JONASSEN et al. "Fatty acid acylated insulins display protracted action due to binding to serum albumin." PEPTIDE SCIENCE: PRESENT AND FUTURE PROCEEDINGS OF THE INTERNATIONAL PEPTIDE SYMPOSIUM, 1ST KYOTO, NOV. 30 1997 (1999), MEETING DATE 197, pages 674-677. EDITOR: SHIMONISHI, YASUTSUGA. PUBLISHER: KLUWER, ORDRECHT, NETH.
D4: BAUDYS et al. "Extending insulin action in vivo by conjugation to carboxymethyl dextran." BIOCONJUGATE CHEM. 1998, vol 9, pages 176-183.
D5: CA 2363712 A1 (CONJUCHEM INC.)

NOVELTY

The instant invention is an insulin derivative comprising an insulin molecule and a reactive group (α, β -unsaturated carbonyl moiety, a succinimidyl-containing group or a maleimido-containing group) for covalently bonding a blood component so as to prolong insulin activity and reduce the number of injections necessary to maintain blood glucose levels in glycemic-related conditions.

Document D1 discloses insulin analogues comprising insulin, or a functional equivalent thereof, conjugated to a pendant molecule at the B1 residue which has an affinity for binding proteins in blood plasma, with thyroxine exemplified as a pendant molecule, to treat glycemic-related diseases. Similarly, D2 discloses an insulin analogue comprising insulin conjugated to 3,3',5-triiodothyroxine at the B1 position allowing for binding with thyroxine binding proteins. D3 discloses the acylation of insulin at the B29 position by fatty acids allowing binding to serum albumin and its use in the treatment of diabetes. D4 discloses an insulin conjugate comprising carboxymethyl dextran (CMD) attached to Gly A1 of insulin which allows the binding of 3-4 insulin molecules (a blood component) to one CMD chain so as to stabilize and prolong insulin action. Finally, D5 discloses a method of derivatizing insulinotropic peptides (GLP-1 and exendin 3 and 4) with reactive groups (maleimido and succinimidyl) with or without a linker so as to bind blood components for the purpose of prolonging the insulinotropic activity. While D1-D4 each discloses insulin derivatives capable of binding blood components for the purpose of prolonging insulin activity *in vivo* to effectively treat glycemic-related disorders and D5 teaches the derivatization of insulin-related hormones with maleimido and succinimidyl, none of the documents disclose an insulin derivative conjugated to the aforementioned reactive groups allowing the covalent bonding of the derivative to blood components. Claims 1-37 are therefore considered novel under Article 33(2) of the PCT.

Continued in Supplemental Box.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Supplemental Box relating to Sequence Listing

Continuation of Box No. 1, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

a. type of material

☒ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☒ on paper

☒ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed

☐ filed together with the international application in electronic form

☒ furnished subsequently to this Authority for the purposes of search and/or examination

☐ received by this Authority as an amendment* on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* If item 4 in Box No. 1 applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded".

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V.

INVENTIVE STEP

Although the prior art discloses insulin derivatives capable of binding blood components and the therapeutic advantages thereof (D1-D4) as well as the derivatization of insulinotropic hormones with maleimido and succinimidyl groups so as to covalently bond blood components for the purpose of protracted activity (D5), a skilled person would not necessarily be lead directly and without difficulty to the instant insulin derivatives capable of covalently bonding blood components. Claims 1-37 are therefore considered inventive under Article 33(3) of the PCT.

INDUSTRIAL APPLICABILITY

Claims 1-22 and 32-36 appear to define subject matter that has industrial applicability under Article 33(4) of the PCT, based on the function of the insulin derivatives of the instant application.

For the assessment of claims 23-31 on the question of whether or not they define subject matter that has industrial applicability, no unified criteria exists in the PCT. Further, the patentability of said claims can depend upon their formulation. Although methods per se defined in claims 23-31 relate to subject matter which this Authority is not obliged to examine under Rule 67.1(iv) of the PCT, the use of the compounds referred to therein for the treatment of glycemic-related disorders appears to represent subject matter that has industrial applicability.